Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Active smoking and COVID-19: a double-edged sword

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We are thankful to Garufi et al [1] for the comments on our recent article published in this journal [2], and we wish to add some further pieces to the intricate puzzle linking active cigarette smoking with severity of coronavirus disease 2019 (COVID-19).

Information that has been garnered so far attests quite reasonably that cigarette smoking may significantly contribute to foster the expression of angiotensin-converting enzyme 2 (ACE2), the primary receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the surface of many cell types, including respiratory epithelia. This fact has been demonstrated by the seminal study of Leung et al [3], and then confirmed by the preliminary investigation of Smith and Sheltzer [4].

Nevertheless, accumulating biological and clinical evidence suggests also that the relationship between active smoking and COVID-19 is not straightforward or unidirectional, and contributes to portray this intricate link as a double-edged sword, so that drawing definitive conclusions may be premature and even misleading, as we emphasized in our previous article [2]. On the one hand, whether cigarette smoking-induced up-regulation of the natural SARS-CoV-2 receptor ACE2 in human cells would increase the likelihood of being infected must be considered. However, to the contrary, increased expression of this enzyme may considerably attenuate the risk of developing the devastating lung and systemic injuries characterizing severe and critical forms of COVID-19 (Fig. 1). ACE2 plays a pivotal role in the pathogenesis of pulmonary disease and its evolution towards respiratory distress, whereby this enzyme catalyzes the conversion of angiotensin II (AngII) into angiotensin 1-7 (Ang1-7), a degradation peptide which strongly counteracts the unfavorable pro-inflammatory, vasoconstrictive, oxidative and fibrotic activity of the parental hormone AngII [5]. AngII levels have been shown to be elevated in COVID-19, correlating with lung injury. Therefore, it seems reasonable to conclude that enhanced expression of ACE2 on the cell surface of the lungs and other organs would cumulatively lower the risk of AngII-mediated tissue injury.

This hypothesis finds some reliable epidemiological ground in a large report by Petrilli et al [6], showing that the prevalence of COVID-19 in tobacco users was significantly higher among patients with no critical COVID-19 illness who could be discharged than in COVID-19 patients who were instead classified as having severe disease (6.7% vs. 4.3%). Overall, this would translate into the evidence that current tobacco users have a nearly 40% lower risk of progressing towards critical COVID-19 illness (odds ratio (OR), 0.63; 95% confidence interval (95%CI), 0.40-1.00). Moreover, in multivariate logistic regression, tobacco use (former and current) was associated with reduced risk of hospitalization (OR, 0.71; 95%CI, 0.57-0.87). Importantly, recent data on approximately 1,500 US patients hospitalized for COVID-19 published by the Centers for Disease Control and Prevention (CDC) COVID-19 Response Team also shows that current smoking may be associated with a non-significant trend toward decreased disease severity [7], whereby the percentage of current smokers was found to be nearly half in patients needing intensive care unit (ICU) admission than in those who do not (1.1% vs. 2.2%; odds ratio 0.51; 95% CI, 0.19-1.36).

Indirect evidence of potential benefits from increasing ACE2 expression for ameliorating the prognosis of COVID-19 has then emerged from studies showing that recombinant ACE2 (rhACE2) is effective to rapidly decrease Ang II and interleukin 6 (IL-6) levels, thus mitigating the pro-inflammatory milieu that is commonplace in patients with acute respiratory distress syndrome [8]. Additionally, interesting evidence has been published in the study of Monteil et al, who experimentally showed that not only could SARS-CoV-2 infection of human blood vessels and kidney organoids be efficiently inhibited by rhACE2, but the administration of this recombinant enzyme could also decrease viral load by a factor between 1,000–5,000 [9].

In conclusion, far be it from recommending cigarette smoking to prevent evolution into severe or critical forms of COVID-19, since the many and multifaceted unhealthy effects of cigarette smoking are well established [10], we endorse the suggestion of Garufi et al [1], that additional prospective studies and collaborative efforts are needed to clarify the complex relationship between smoking and COVID-19 (Fig. 1).

Declaration of Competing Interest

All authors have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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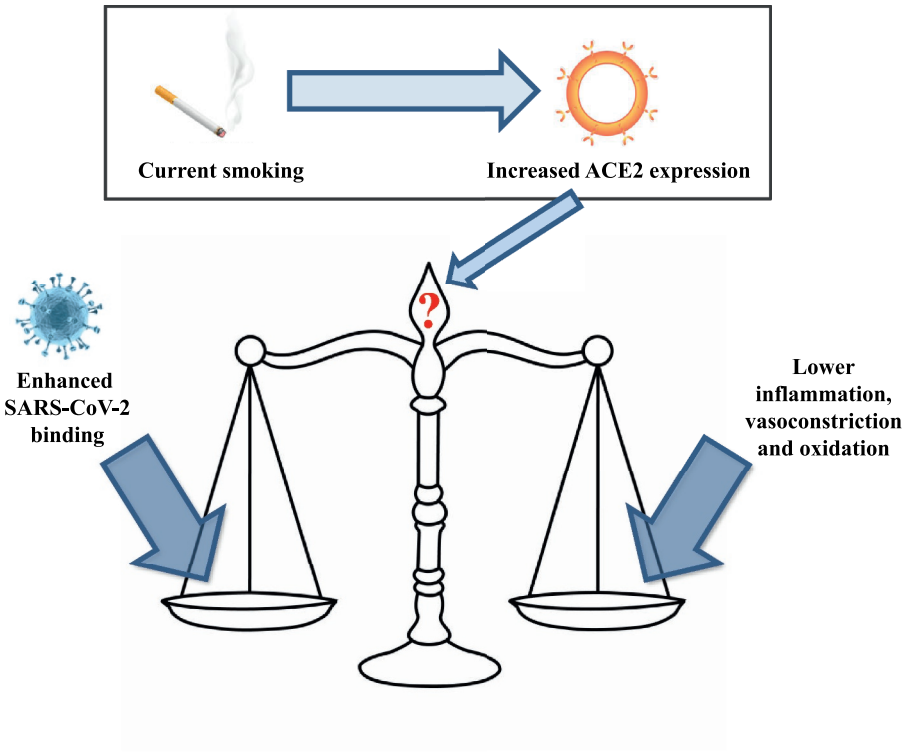

Fig. 1. The intricate and still enigmatic relationship between current smoking and coronavirus disease (COVID-19).
ACE2, angiotensin converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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